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Dr. Jean Marx
Science
1515 Massachusetts Avenue, N.W.
Washington, D.C. 20005

Dear Dr. Marx:

I wanted you to know that I enjoyed your recent story about oncogenes, and I enclose, for your interest, the forthcoming paper that substantiates some claims for mutations in c-myc in bursal lymphomas to which you allude at a couple of points. (There are, incidentally, no hard feelings here about anonymity: I am enough of a journalist to know you can't cite everyone.) It may be some time before the full significance of such mutations can be assessed. We know that normal c-myc, linked to a strong promoter, is sufficient to complement a mutant ras gene in the assay Weinberg and associates have devised. Leder and colleagues have recently found that the translocated c-myc alleles in Burkitt's lymphomas do have various other mutations, but most (if not all) involve non-coding regions (in contrast to the results just published by Rabbitts). Resolution of the issues raised by these observations may require a better understanding of mechanisms of mutagenesis in higher eukaryotes: if translocations and insertion mutations transiently promote high error rates, these "secondary" mutations may simply accompany the primary lesions. If they occur later, it would seem necessary (as we argue in the enclosed manuscript) that they be selected for as a consequence of their effects upon growth potential.

What at least seems clear--and was well-stated in your article--is that the field has risen beyond the misleading simplicities of a qualitative versus a quantitative model for activation for all oncogenes. Each oncogene seems to have its own peculiarities. You might want to keep your eye on a forthcoming issue of Cell in which Verma's group demonstrates a surprising requirement for the activation of c-fos. In addition, recent work by Spandidos and Wilkie suggests that over-expression of a mutant ras gene can transform primary rodent cells without the collaborating oncogene that Weinburg's work would predict to be required. It is apparent that our new ability to manipulate doses of gene products is likely to confuse traditional assignments of phenotypes to genotypes.

With best regards,

Harold E. Varmus, M.D.
American Cancer Society
Research Professor

Enclosure

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